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Smart Materials for Wearable Healthcare Devices

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Abstract

Wearable devices seem to have great potential that could result in a revolutionary non-clinical approach to health monitoring and diagnosing disease. With continued innovation and intensive attention to the materials and fabrication technologies, development of these healthcare devices is progressively encouraged. This chapter gives a concise review of some of the main concepts and approaches related to recent advances and developments in the scope of wearable devices from the perspective of emerging materials. A complementary section of the review linking these advanced materials with wearable device technologies is particularly specified. Some of the strong and weak points in development of each wearable material/device are clearly highlighted and criticized.

Keywords: wearable device, smart materials, healthcare, diagnostic biomarkers, physiological index

1. Introduction

Wearable devices are apparatuses that can be worn directly on the skin in different parts of the body. These devices have gained considerable attention owing to their ease of collection of crucial information in real-time regarding a wearer's health, both continuously and non-invasively [1–7]. In contrast to the traditional non-invasive methodologies (e.g., X-ray, type-B ultrasonic, nuclear magnetic resonance (NMR)), non-invasive diagnosis implemented by wearable devices creates new opportunities for remote and continuous healthcare monitoring in non-clinical settings [5, 8], with the ability to detect developing diseases at intervals between routine examinations. The use of wearable healthcare devices also encourages people to take greater interest in their own healthcare in a more convenient and cheaper way, thereby improving their compliance.

Wearable devices are becoming smaller and more mobile with time, opening new alternatives to traditional ways that providers have interacted with patients, carried out tests, collected data and delivered treatments [9–11]. Wearables come in many forms; there are smart wristbands [12], watches [13], shirts [14], shoes [15], headbands [16], eyeglasses [17] and necklaces [18], among others. Most of them contain sensors that gather raw data that is fed into a database or software application for analysis. Analysis typically triggers a response that would, for example, alert a physician to contact a patient who is experiencing abnormal symptoms, or might send an appreciative message when an individual achieves a fitness or diet goal [11].

Recent insights into wearable devices have resulted in rapid development of various kinds monitoring different parameters, such as pressure/strain, body vital signs (e.g. heartbeat rate, respiration rate and temperature) and biomarkers that can be found either in body fluids (e.g. saliva, sweat and tears) or in skin odor and breath [19–23]. Among these reported wearable healthcare settings, skin-based wearable devices have considerable advantage in allowing simultaneous monitoring of multi-physiological indexes and biomarkers [19, 21, 22, 24]. By continuous or frequent detection of the level of physical markers (e.g. pressure pulses and body temperature) using different sensing techniques, wearable devices can provide one of the most comprehensive feedbacks on human health states [7, 8, 19, 22, 24–32]. Perspiration contains a diversity of chemical species (e.g. minerals, trace elements, lactic acid, urea and volatile organic compounds) that can be detected and monitored in sweat, which can assist in determining the health status of a person. A good example of the potential of sweat diagnostics is the detection of cystic fibrosis [33, 34], currently in clinical use [35]. However, small sample volumes, dilution of analytes and variability in the measurement of concentration are some of the challenges that are encountered using sweat for diagnosis. **Table 1** summarizes the different physiological indexes and diagnostic biomarkers using wearable devices. As inferred in **Table 1** for gathering broad information of the health status, the skin-based wearable devices should integrate multiple sensing features. Consequently, the performance of a wearable device depends heavily on the proper sensing characteristics of its integrated sensing parts.

Although many challenging issues are of concern, developing technologies proposed in the last few years significantly enhance the practicability of applying these wearable devices in clinic use and academic research. One of the main reasons for the advance of wearable devices is covertly the rapid emergence of new materials with interesting properties [19, 23, 24]. As a result, modern wearable devices are becoming cheaper, smaller and more reliable. Several reviews on these aspects have already been published [38–40]. The aim here is to present the current state of non-invasive skin-based wearable devices from the perspective of materials science and engineering. In view of these emerging skin-based wearable devices that are expected to meet diverse healthcare applications, smart materials used for these purpose should be compliant with the following basic criteria:

- **Highly sensitivity to subtle changes in the physiological index:** subtle change in the physiological index, for example, body temperature, may be an early indicator of health problems. For the purpose of catching very slight changes in the human body, stimuli-responsive materials used in skin-based wearables should be very sensitive. For instance,

Sample source	Physiological parameter	Sensing devices	Refs.
Temperature	<ul style="list-style-type: none">• T_{body}^a	<ul style="list-style-type: none">• Resistometric sensor• FET^b	[7, 8]
Odor	<ul style="list-style-type: none">• VOCs^c	<ul style="list-style-type: none">• Resistometric• Colorimetric sensor	[19]
Pressure/strain	<ul style="list-style-type: none">• Heart/respiration pulse• Motion posture	<ul style="list-style-type: none">• Resistometric sensor• Capacitive sensor• Piezoelectric sensor	[24]
Sweat	<ul style="list-style-type: none">• Metal ions• Lactate• Uric acid• pH• Ammonium• Chloride• Skin humidity	<ul style="list-style-type: none">• Potentiometric sensor• Amperometric sensor• Voltammetric sensor• Resistometric sensor• Colorimetric sensor	[27, 29–32, 36, 37]

^a T_{body} = Body temperature
^bFET = Field effect transistor
^cVOC = Volatile organic compound

Table 1. Typical non-invasive skin-based wearable healthcare devices.

- thermal-responsive materials used in body temperature sensors should sense down to 0.1°C variation, obviating missing any sign of health risk.
- **Adequate detection limit:** stimuli and/or analytes obtained from human skin are generally at low level regime, for example, pressure of pulsing artery is typically within several hundreds of Pa, which gives the benchmark for designing wearable pulsing sensors. Consequently, an adequate detection limit is particularly required by the responsive materials for these stimuli and/or analytes. Since the level of analytes coming from human skin is usually lower than that of analytes obtained directly from tissue or body fluid (excluding sweat), detection limit of these smart materials dedicated in the design of skin-based wearables is even lower compared with those wearable counterparts developed for other uses (e.g. implantable devices, breath sample analyzer, etc.).
 - **Compatible with human skin:** materials that are featured as flexible, stretchable and less irritating are especially to be considered in these skin-based wearables, largely due to their

unique biocompatibility with soft and moist skin. Flexible and stretchable elastomers are more suitable for fabricating strain-responsive devices.

Owing to the continuous increase in the essential requirements of and interest in, the skin-based wearables, an update on the relevant materials is presented in this review, with an emphasis on novel materials and sensing techniques, with regard to their advantages, limitations, challenges and future trends. A comprehensive description of the unique technique in accessing health conditions by monitoring skin biomarkers and physiological parameters has also been also particularly in focus.

2. Smart materials for wearable healthcare devices

2.1. Wearable temperature sensors

To meet the requirements of non-invasive and quantitative monitoring of body temperature, wearable temperature devices are required to be flexible, biocompatible, lightweight and highly sensitive within temperatures range 35–42°C [41, 42]. Several temperature-sensing devices have been invented in the past, but flexible wearable temperature-sensing devices (**Table 2**) are mainly limited to thermally resistance (resistometric) and thermally sensitive field-effect transistor (FET) transduction mechanisms. While the operation mode previously relied on resistance changes of the sensing elements according to the temperature change, the latter relies on detecting FET transfer characteristics as a result of thermal effects [7, 41–48, 50, 53].

The attractive advantages of low-cost, simple configuration and ease of mass production made thermal-resistance-based temperature devices the most popular as skin-mounted sensors [43–46, 48]. These devices relay thermal expansion and/or variation in temperature coefficient of resistance (TCR) induced by changing temperature [46]. An acceptable thermal expansion coefficient and TCR of metal and metal oxides have become available and have been used in the past decades [45, 48, 54]. A representative metal-based sensing element for tracking skin temperature is gold foil or nanoparticles that possess a desirable TCR [45, 54]. For TCR-based devices, gold has good ductility and can be deposited on a range of substrates, including glass, SiO₂ and flexible polymer [45, 54]. This allows the design of ultrathin [55, 56] and flexible wearable temperature devices suitable for a range of complex measurement under different conditions.

An example of a successful wearable temperature sensor is the epidermal device designed for continuous thermal monitoring of human skin (**Figure 1a**). With integrating 4 × 4 TCR (Cr/Au) sensor array on a thin elastomeric substrate, this ultrathin conformal device gives reliable performance and minor deviations [45, 61]. However, the sensing range for most of metal-based sensing elements is limited to relatively high temperatures (normally >42°C) because of their low thermal-response [46]. Inadequate sensitivity of metal-based sensing elements also brings the need for sophisticated measurement electronics for increasing signal-to-noise ratio. Hence, to increase the thermal response range and improve the sensitivity of these devices, and increase efficiently the signal-to-noise ratio, alternatives have been devised, one being

Sensing materials	Working principle	Sensitivity	Range of measured temperature	Refs.
Si nanoribbon	Resistometric	N.M. ^a	37–58 (°C)/310.15–331.15 (K)	[41]
MWCNT/PVBC-Et ₃ N ^b	Resistometric	−0.004 K ^{−1}	20–40 (°C)/293.15–313.15 (K)	[43]
MWCNT/SEB ^c	Resistometric	−0.028 K ^{−1}	20–50 (°C)/293.15–323.15 (K)	[44]
Cr/Au	Resistometric	N.M.	23–31 (°C)/296.15–304.15 (K)	[45]
GNWS/PDMS ^d	Resistometric	0.214°C ^{−1}	35–45 (°C)/308.15–318.15 (K)	[46]
Graphite/acrylate copolymers	Resistometric	N.M.	37–58 (°C)/310.15–331.15 (K)	[47]
Ni-filled PEO/PE ^e	Resistometric	0.3 V°C ^{−1}	35–42 (°C)/308.15–315.15 (K)	[48]
SWCNT/self-healing polymer	Resistometric	N.M.	20–80 (°C)/353.15 (K)	[49]
R-GO/PU ^f	FET	0.09°C ^{−1}	30–80 (°C)/303.15–353.15 (K)	[7]
R-GO	FET	6.7 nSK ^{−1}	30–80 (°C)/303.15–353.15 (K)	[50]
P(VDF-TrFE)/BaTiO ₃ ^g	FET	N.M.	35–40 (°C)/308.15–313.15 (K)	[51]
Ag/pentacene	FET	N.M.	15–70 (°C)/288.15–343.15 (K)	[52]

^aN.M. = Not mentioned.

^bMWCNT/PVBC-Et₃N = Multi-wall carbon nanotubes/poly(vinylbenzyl chloride) derivative with triethylamine.

^cMWCNT/SEB = Multi-wall carbon nanotubes/poly(styrene-*b*-(ethylene-co-butylene)-*b*-styrene).

^dGNWS/PDMS = Graphene nanowalls/polydimethylsiloxane.

^eNi-filled PEO/PE = Ni-filled polyethylene oxide/polyethylene.

^fR-GO/PU = Reduced graphene oxide/polyurethane.

^g(VDF-TrFE)/BaTiO₃ = Poly(vinylidene fluoride-trifluoro-ethylene)/BaTiO₃.

Table 2. Performance of typical examples in measuring epidermal temperature.

based on carbon nanotubes (CNTs) where resistance is strictly dependent on temperature. By dispersing proportional amounts of CNTs into specific polymer such as poly(styrene-*b*-(ethylene-co-butylene)-*b*-styrene; SEBS), flexible sensing composites had very high sensitivity to changes in ambient temperature from 20 to 40°C [43, 44].

Compared to thermal resistance-based devices, FET-based temperature devices have greater sensitivity, and are easily incorporated into integrated circuits of convenience in signal amplification [7, 42, 50]. By applying thermal-responsive materials as an active channel, electrode or gate dielectric layer into the FET structure, promising results in determining skin temperature have been achieved. Few examples of FET-based temperature sensors include graphene-based sensing elements, metal-polymer hybrids, inorganic-polymer hybrids [7, 42, 47, 50, 51, 53]. Owing to the appropriate and adjustable thermal activation energy of the charger carrier for these thermal-responsive materials, the detection limit of the FET-based temperature devices can reach milli-Kelvin [47]. The inherent characteristics of FET-based devices also help in the precise sensing signals, with a deviation of <0.1°C [47].

Inadequate thermal-response, unsatisfactory stability and significant interference from the ambient environment are all challenging issues for wearable temperature devices [43, 46, 50].

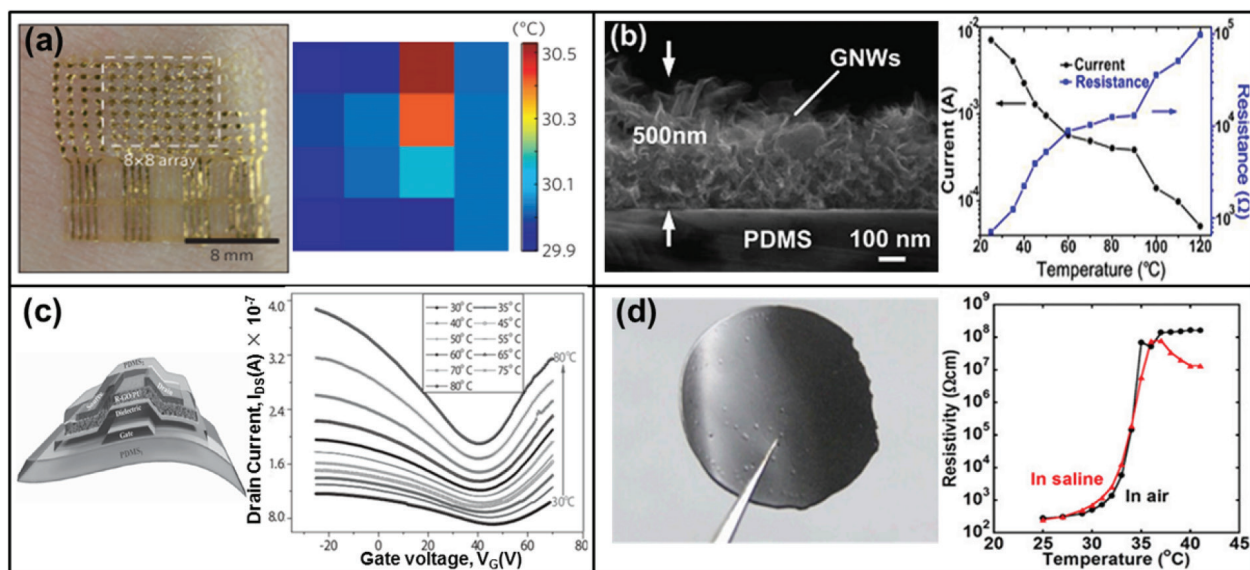


Figure 1. Schema of temperature sensors. (a) Image and the sensing performance of a 4×4 TCR sensor array after application to the skin using a water-soluble adhesive tape based on polyvinyl alcohol. (b) Cross-section SEM image of GNWs on PDMS and its “current and resistance versus temperature” curves. (c) Schematic of the TS-gated device and its response to temperature. (d) Photograph of a film of copolymer with graphite filler, with the temperature dependence of the resistivity of the temperature sensor. Reconstructed from Refs.[57–60].

Latterly, graphene nanowalls (GNWs) in combination with polydimethylsiloxane (PDMS) have been used as the sensing chip in a thermal-resistive sensor (**Figure 1b**) [46]. In comparison to conventional temperature sensors, this device has a sensitivity over $108.6 \Omega \text{ } ^\circ\text{C}^{-1}$ between 35 and 45°C , which is sufficient to monitor human body temperature. Further evidence proves that the high response of the sensor can be attributed to the excellent TCR (0.214°C^{-1}) of GNWs and large expansion coefficient of PDMS [46]. Stability of these temperature devices has been many times reported, who found that the transition of morphology and phase of sensing elements during cooling-heating cycle is the main reason for irreproducibility of a thermal response [44, 48]. Adsorption of water vapor and/or ambient gas species is another crucial reason that generates hysteresis and causes significant interference [50]. Consequently, thermally stable materials are screened and extra encapsulation layers are added to decrease hysteresis, thereby improving stability and enhancing reproducibility (**Figure 1c**) [44, 48, 50]. Taking these materials from the lab to the technological/industrial benchmark would require advanced printing techniques. A graphite-polymer-based ultrathin thermometer of $15 \mu\text{m}$ thickness that could be accomplished by such simple print and press method is a good example for fabrication of large-area stretchable and transparent wearable temperature devices in the future. These fabricated thermometers should be able to measure temperature precisely between 25 and 50°C (**Figure 1d**) [47].

2.2. Wearable strain sensors

Wearable strain sensors could be useful for the detection and monitoring of movement-based signals, such as heartbeat and respiration rate. Generally, wearable strain devices should be lightweight, reliable, flexible and stretchable to match the mechanical properties of human skin. Sensitivity of these strain sensors must also be in line with their diverse healthcare

applications. For instance, mean value of feet pressure for adults mostly ranges from 140 to 868 kPa [62], whereas systolic pressure (artery pulse) for healthy persons is within 0.67–5.32 kPa (5–40 mmHg) [63]. This suggests that high sensitivity in a low-pressure regime (perhaps <10 kPa [64]) is required for strain sensor trying to detect arterial pulse. To date, many working models for strain devices have been developed [65]. Among them are flexible and stretchable devices based on piezoresistive, piezocapacitive and piezoelectric principles seem to be closer to practical implementation, due to their relatively simple sensory configuration, uncomplicated read-out systems and acceptable dynamic performance [24, 66–68].

2.2.1. Piezoresistive-based strain sensors

Piezoresistive-based strain devices are typically composed of electrically conductive sensing films coupled with flexible substrates. When the structure of the device is deformed, changes in the microstructure of sensing films lead to changes in electrical resistance as a function of applied strain. Metal-based foil and graphitic-based sensing networks (e.g. InGaZn and graphene) are widely used in pressure/strain sensing [73–75]. In conductive networks, electrons can pass through overlapped nanomaterials within the percolation network. Stretching or bending in the conductive network results in disconnection between overlapped areas and thereby loss electrical connection; consequently, there is an increase of the electrical resistance of sensing film. Another known strain-responsive mechanism is crack propagation, that is, cracks originate and propagate in brittle thin films coated on the top of soft polymer layers upon stretching [20]. Generally speaking, the sensitivity (gauge factor) of the conventional metal foil-based strain device is in the range of 2–5 (a.u.) and semiconductor-based strain sensors might be 100 or greater. The value of sensitivity for flexible strain devices can be in the range of 1–100 s, depending on the sensing mechanisms, materials and micro/nanostructures [20].

To meet the demand of practical healthcare applications, a proof-of-concept wearable pressure device based on ultrathin Au nanowires (NWs) has been developed (**Figure 2a**) [76]. The Au NWs directly coated on a tissue paper can detect pressure forces as low as 13 Pa with high sensitivity (41.1 kPa^{-1}). Furthermore, the devices also provide fast response times (<17 ms) and high stability (450,000 loading–unloading cycles) [76]. A similar strategy has also been used in the design of piezoresistive strain devices comprised of other sensing elements, for example, graphene [74]. Furthermore, these prototypes give excellent performance in real-time monitoring of human blood pulses and detection of music motion to confirm their usefulness in healthcare applications [74, 76].

Strain sensors based on the piezoresistive conductive polymer (CP) and their composites have also been receiving considerable attention due to their excellent flexibility and biocompatibility [77]. These CP composites are usually based on polymeric matrix filled with stainless steel fibers (SSFs) and carbon nanotubes (CNTs) [57]. CP and their composites generally have robust piezoresistive behavior for a long period time under the temperature ranging from -50 to $+200^\circ\text{C}$ [57]. Note that their piezoresistivity is closely dependent on the conductive phase content. When this is low, piezoresistivity monotonically increases; in contrast, the piezoresistivity is monotonically decreasing at high conductive phase content [58]. Such flexible piezoresistive CP or CP composites are attractive candidates for wearable devices, for instance,

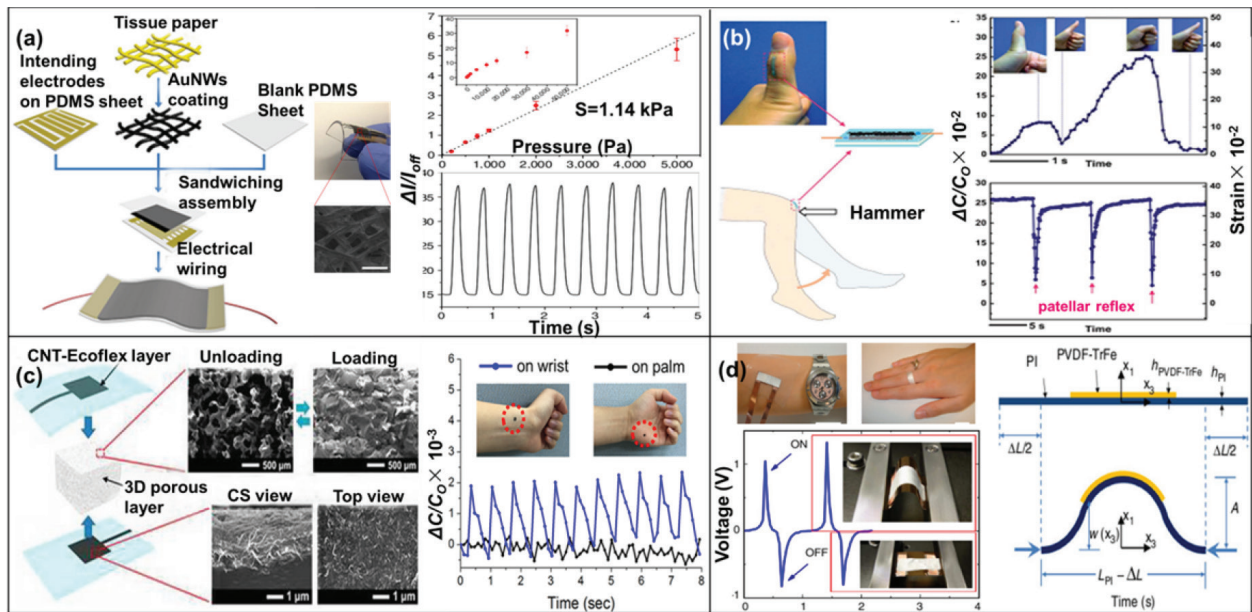


Figure 2. Strain-responsive devices based on emerging materials and fabricating technology. (a) AuNWs-coated tissue paper and (b) piezocapacitive-based strain device composed with AgNWs. (c) Three-dimensional (3D) microporous dielectric elastomer for a piezocapacitive strain device. (d) Piezoelectric devices based on aligned arrays of nanofibers of PVDF. Reconstructed from Refs. [69–72].

through coating poly(3,4-ethyl-enedioxythiophene–poly(styrenesulfonate) (PEDOT:PSS)/polyurethane composite polymer on the spring-like compressible micro-pyramid-structured substrate, a stretchable strain sensor with high sensitivity has been developed [59]. The sensor had a sensitivity of 10.3 kPa^{-1} when stretched by 40%, which is sufficiently sensitive to detect human pulse pressure (23 Pa) [59]. Furthermore, its suitability in non-invasive healthcare applications is validated by showing excellent piezoresistivity and a fast response rate in measuring the primary features of the waveform in the human pulse.

It should be noted that beyond those conventional strain-responsive materials, stretchable silicon has received considerable attention from researchers because of its superior response to strain [60]. This silicon can be reversibly stretched and compressed to a large extent without damage, a new finding that might provide opportunities to design tunable structures that are compatible with mechanical strain [60]. Miniaturization and simplicity of configuration of the devices, as well as decreasing power consumption, is another challenging issue. Hence, a high-resolution unpixelated smart device was proposed for sensing stimuli. The sensing film of the device is constructed from two parallel GNP strips with antiparallel sensitivity gradients [78]. This design enables the device not only to detect the loaded strain, but also to discriminate the spatial position of the strain [78]. The gradient design of the sensing film can remarkably decrease the complexity and power consumption of a future strain-responsive device.

2.2.2. Piezocapacitive-based strain devices

Piezocapacitive-based strain devices use a highly compliant dielectric layer sandwiched between a pair of stretchable electrodes. Applied strain changes the distance between two electrodes, which results in a change of capacitance [24]. For instance, a piezocapacitive strain

sensor composed of silver nanowire (AgNWs), Ecoflex, liquid metal and PDMS was built for finger flexing and knee motions among other body movement tracking (**Figure 2b**) [79]. Quick response (<40 ms) and good pressure mapping function was discovered during the examine process; and the designed piezocapacitive strain device has satisfactory wearability when mounted on the human body.

Besides these conventional strain devices, a transparent flexible pieocapactive pressure/strain sensor has been developed by Lipomi et al. [80]. The pieocapactive sensor, made by spraying transparent carbon nanotube on PDMS, gave a desirable performance in detecting pressure down to ~50 kPa [80]. Note that this transparent piezocapacitive skin-like strain sensor is extremely compliant mechanically, physically robust and easily fabricated, although it is less sensitive than its other counterparts.

In contrast to those piezoresistive counterparts, piezocapacitive strain devices have high linearity, stretchability and low hysteresis, but suffer from low sensitivity. Thus, a 3D microporous dielectric elastomer with giant piezocapacitive effect was used to construct a pressure device (**Figure 2c**) [81]. Due to the presence of micropores within the elastomeric dielectric layer, the resulting piezocapacitive pressure device is highly deformable by the minimal amount of pressure, leading to a marked increase in sensitivity. The gradual closure of micropores under compression also increased the effective dielectric constant, thereby enhancing sensitivity. The 3D microporous dielectric layer with serially stacked springs of elastomer bridges can cover a much wider range of pressure than those of previously reported micro-/nanostructured sensing materials. This proof-of-concept can help in monitoring both ultralow and high levels of human activity. Noteworthily, materials with unique microstructure will enhance their piezocapacitive performance. Compared with those piezocapacitive materials with flat surface, the pressure sensor comprised of pyramidal dielectric elastomer significantly enhanced blood pulse monitoring and force tracking [82]. Similar improvements have also been investigated for piezoresistive elastomer with hollow-sphere [83], thickness-gradient [84] and pyramidal microstructures [85], implying an efficient approach to improve the performance of strain sensors by well-designed strain-responsive materials.

2.2.3. Piezoelectric-based strain sensors

Piezoelectric-based strain sensors detect changes in pressure or strain; in particular, sensing signal (voltage) is only generated by dynamic changes of applied strain or force. Piezoelectric materials, especially certain crystals (e.g. ZnO and LiNbO₃) and some ceramics (e.g. BaTiO₃ and Pb(Zr_{1-x}Ti_x)O₃ (PZT)), generate a voltage potential when the crystal lattice is deformed [86, 87]. The sensitivity of piezoelectric materials depends on their crystal structure and the voltage generated is directly proportional to the applied strain. These sensors have very good high-frequency responses, which makes them ideal for measuring dynamic forces [88]. To match the mechanical properties of human skin, recent piezoelectric materials used in wearable devices are mechanically flexible [87, 89, 90]. These flexible piezoelectric materials can be based on either rigid piezoelectric materials embedded in a flexible substrate or a piezoelectric polymer film.

Compared with piezoresistive- and piezocapacitive-based strain sensors, strain devices comprised of piezoelectric materials have greater dynamic durability. The nature of good high-frequency response to an applied strain makes this device more suitable for measuring vibrations. For example, piezoelectric-based strain sensors could be installed in a smart watch for monitoring heartbeat rate. However, the dynamic piezoelectric sensing mechanism disallows them from measuring static forces. A classic piezoelectric material commonly used in flexible strain devices is poly(vinylidene fluoride; PVDF), a piezoelectric polymer that has considerable flexibility [90]. Its flexibility and high piezoelectric factor make PVDF an attractive material for flexible strain devices. For example, Persano et al. (**Figure 2d**) reported on aligned arrays of nanofibers of PVDF [91]. Free-standing 3D architectures of aligned arrangements of PVDF fibers have been designed (**Figure 2d**); furthermore, the polymer chains inside the fibers adopt strongly preferential orientations [91]. This microstructure enables ultra-high sensitivity in measuring pressure, even at exceptionally low values (0.1 Pa); in particular, exceptional piezoelectric characteristics offered by these devices indicate an application in monitoring human motion.

2.3. Wearable devices for recording electrical conductivity through the skin

Wearable devices that detect tiny electrical changes on the skin could be helpful for monitoring the electrical activity of heart to locate an arrhythmia (abnormal heartbeat). These results can help one or one's doctor to decide whether you need medicine, a pacemaker, an implantable cardioverter defibrillator (ICD), cardiac neural ablation or some other surgery. For wearable and accurate monitoring of electrophysiological signals in a variety of everyday conditions, reliable biopotential-capturing electrodes that are reusable with long-term stability required, and they should also not cause skin irritations or allergic reactions.

To date, disposable silver/silver chloride (Ag/AgCl)-gelled electrodes are most commonly used, but these electrodes have limited storage time (<1 year) and are not reusable [96]. The best possible alternatives are flexible dry electrodes, which are usually made of polymeric- and textile-based materials [69, 96–98]. For instance, after patterning a metal layer on a thin PDMS substrate, a biocompatible and flexible PDMS-based (polymetric) electrocardiogram (ECG) recording device can be obtained (**Figure 3a**) [97]. In the case of textile-based electrodes, these are normally fabricated by knitting, weaving, embroidering and non-weaving methods. **Figure 3b** shows photographic images and comparison of the response of the textile-based dry electrode and (Ag/AgCl)-gelled electrode in wearable ECG recording devices. These flexible dry electrodes in general are more skin compatible compared with those of gelled electrodes (**Figure 3**) [69, 96–98]. However, disturbances to ECG signals caused by body movement can often appear. Despite larger disturbances due to movement, these flexible dry electrodes cause relatively little irritation or itches on human skin compared with (Ag/AgCl)-gelled electrodes. After wearing the polymeric dry electrodes for 7 days, no significant changes on skin were seen (**Figure 3a**); however, the skin under the (Ag/AgCl)-gelled electrode turned red and became itchy in two subjects. In conclusion, these newly proposed dry electrodes have comparatively good fidelity and are comfortable regarding body contact as well as being acceptable in long-term stability, indicating broad applicability to the ubiquitous field of biosignal monitoring.

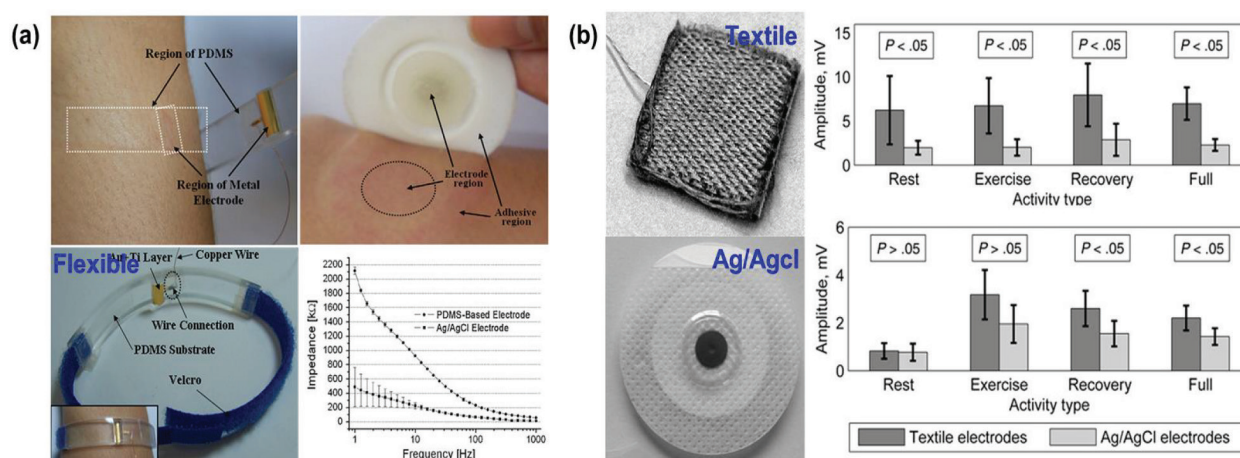


Figure 3. Typical examples of flexible dry electrodes for ECG signal recording. Photographs of (a) polymeric- and (b) textile-based electrodes, and their response to biosignals compared with those of commercial Ag/AgCl electrodes. Reconstructed from Refs. [92–95].

2.4. Wearable sensors for analyzing sweat metabolites

Levels of sweat metabolites (such as lactate and uric acid) and electrolytes (metal ions, such as sodium and potassium), as well as skin humidity, are useful physiological parameter indirectly reflecting health status of an individual, and can potentially be used to probe body conditions by non-invasive monitoring [21, 23, 33, 34, 37, 99]. **Table 1** summarizes the use of sweat body fluids as physiological biomarkers [7, 8, 27, 33]. The concentration of uric acid and urea in sweat is much higher in uremic patients [100]. Levels of skin humidity and pH of sweat, as well as its electrolytes, are important indicators of dehydration and electrolyte loss during exercise [101]. Accordingly, sweat-based wearable devices are required for monitoring these non-invasive health states.

To date, sweat-based healthcare devices are mainly based on an electrochemical sensing principle, owing to the low-cost, high-performance and excellent portability of electrochemical devices [21, 23]. **Figure 4a** shows the configuration of a generally reported electrochemical sweat-based device [102]. Three electrodes are printed on the flexible substrate and, as might be necessary, a fourth electrode can be present, that is, a working electrode (WE), a counter electrode (CE, sometimes as anode), a reference electrode (RE), and a cathode. WE and CE are normally composed of conductive materials, such as carbon black, CNTs, Pt black, modified Ag or Au, etc. [21, 102, 103]. Ag/AgCl is usually used as the RE. Conformal contact between the electrode surface and the skin is necessary to ensure efficient functioning of the devices. Accordingly, substrates for these devices should be made of fabric (e.g. wool, cotton or nylon) or flexible plastics [21]. Unique technology is required for fabricating firm electrodes/substrate configuration.

Figure 4b–d shows three typical approaches [21, 23, 37, 70, 103–105] for attachment of electrodes to a flexible substrate or skin [21, 23]. The first approach relies on screen-printed electrodes [23]. This approach has been massively employed in production due to its low-cost, industrial-scale fabrication of robust electrodes on different substrates. The geometries and thickness of the electrodes

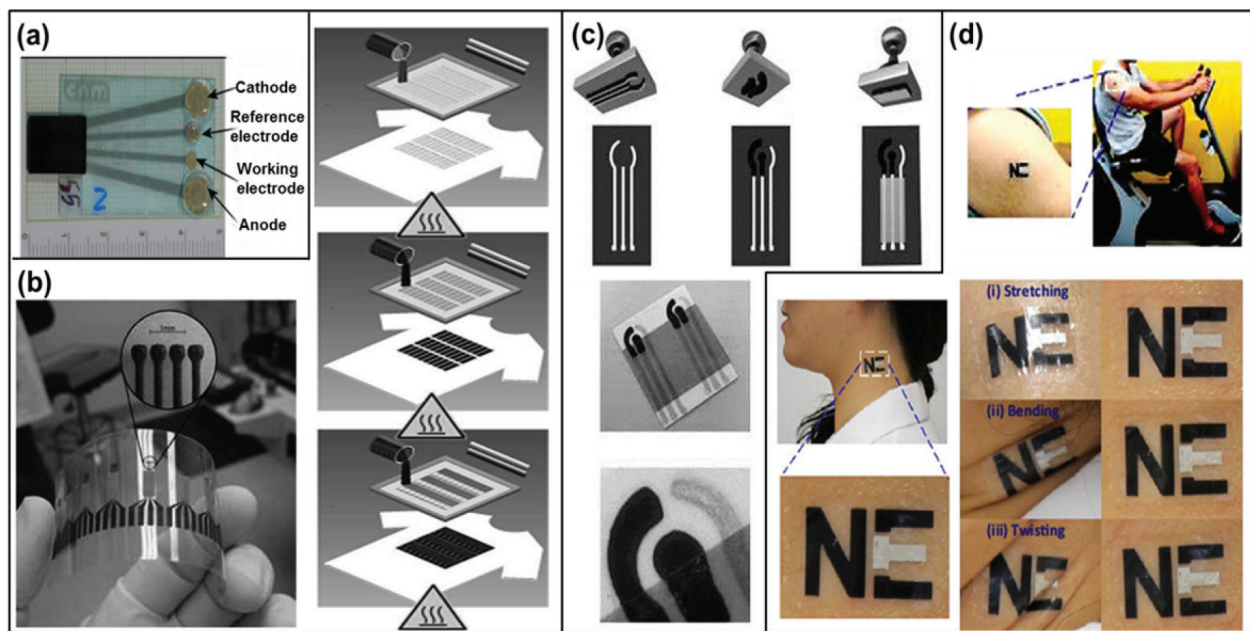


Figure 4. General fabrication technology of sweat-based wearable devices. (a) Primary configuration of the sweat-based electrochemical wearable devices. (b) Steps involved in screen printing thick-film electrochemical devices. Left of **Figure 4b**: Representative design of flexible device fabricated by a screen-printing technique. (c) Preparation progress of stamp transfer electrodes. (d) Typical example of a tattoo-based wearable device. Reconstructed from Refs. [21, 23].

can be readily adjusted by changes of the screen mask to meet the design requirements of the wearable device. However, preparation of wearable devices by screen printing involves several complicating issues; for instance, the influence of manufacturing conditions and substrate properties, as well as the composition of the ink, need to be taken into consideration, since these factors significantly determine the performance of the devices. Generally, the natural properties of substrates must be compatible with the printing process and the specific operational environment. Some necessary modification, for example, doping of the noble catalyst, may be required for the inks to obtain specific functionality. The annealing temperature also requires optimization to avoid undesired deformation of the electrode and substrate. The left part of **Figure 4b** depicts the screen-printed microelectrodes on polyethylene naphthalate (PEN) for dopamine detection, suggesting the convenience of depositing responsive materials by this approach.

The second approach used for attachment of electrodes to a flexible substrate or skin relies on stamp transferred electrodes [23]. The pattern-transfer technique is very useful in fabricating sensing materials on a non-planar substrate, particularly on uniformly non-planar substrates. **Figure 4c** shows details of the stamp transfer process. It is known that, through pattern-transfer technique, responsive materials are highly compatible with irregular substrates possessing diverse surface morphologies (e.g. skin), without compromising the structural integrity of the pattern. Stamp transferred electrodes notably give better performance than those fabricated by screen-printing technique [23]. This fabricating technique provides a novel method to form the ink-based printable materials on non-planar and oversized surfaces incompatible with standard screen-printing methods.

The third approach used for attachment of electrodes to a flexible substrate or skin relies on epidermal suspended electrodes [21]. The rationale behind this approach is to deal with the major

problem for traditional wearable device by restricted intimate contact with the skin at limited regions – something that can be solved if the sensing electrodes can be directly attached on the skin. Inspired by tattooing, the strategy of using elastomeric stamps or the tattoo technique to form electrodes directly on human epidermis has been proposed. The strategy includes steps of screen printing of conductive and insulating inks on commercial, temporary tattoo-base paper, to form the electrodes and/or devices, and then flip and apply the fabricated tattoo or printed electrodes to the skin. To adapt for mechanical stress and overcome the potential deformations due to bodily movements, it was suggested that finely dispersed carbon fibers should be incorporated into the tattoo-based devices. Numerous results showed the success and convenience of applying this new technique in preparing electrodes and/or wearable devices on the skin. Among these examples, a classic prototype reported by Jia et al. [71] was noteworthy. In the prototype (**Figure 4d**), an enzymatic tattoo amperometric biosensor was built for continuously monitoring lactate levels in the perspiration as a biomarker of physical stress. This flexible, printed, temporary-transfer tattoo, electrochemical biosensor adhered well to the skin and had acceptable selectivity to lactate, with linearity up to 20 mmol/L. In particular, the device had commendable resilience against continuous the mechanical deformation expected from epidermal wear.

Simultaneous screening of target biomarkers is helpful in ensuring the accuracy of measurements. Consequently, multifunctional wearable devices combining sensing and therapy have been particularly a focus of attention. Through providing sufficient information of heater, temperature, humidity, glucose and pH, as well as several chemicals in sweat, these multifunctional wearable devices (e.g. graphene-based electrochemical device) give a comprehensive profile of health status [27, 106]. On account of these attractive results, it is expected that, through combination of advanced materials science and these innovative preparation techniques, sweat-based wearable devices could possibly alert traditional disease prevention.

Spontaneously measuring chemical and ECG parameters will provide more comprehensive information about health status; however, most of the reported wearable healthcare sensors can only measure chemical or ECG parameters. To obtain fuller information of the human body, these monofunctional sensors need to be integrated into a sensor matrix, which increases the complexity of fabrication. An alternative strategy to resolve this issue is to design sensors that can be used for monitoring chemical and ECG parameters spontaneously. Based on this strategy, a wearable chemical-ECG hybrid biosensing system is proposed for real-time health and fitness monitoring [107]. The proposed system should give a desirable performance in simultaneously sensing lactate (0–28 mmol/L) and monitoring ECG parameters [107]. Such proof-of-concept opens a new way in designing flexible smart sweat-based healthcare devices.

2.5. Wearable sensors for detection of volatile biomarkers

Numerous experimental data have verified the robust correlation between volatile organic compounds (VOCs; organic compounds that have a high vapor pressure under ordinary room temperature conditions) and health status [72, 92–95, 108–143], indicating that changes in VOC profiles (amount and/or species) of human skin can be used for early diagnosis and warning of potential health risks [109, 110, 112]. The ideal approach to track VOCs exuded

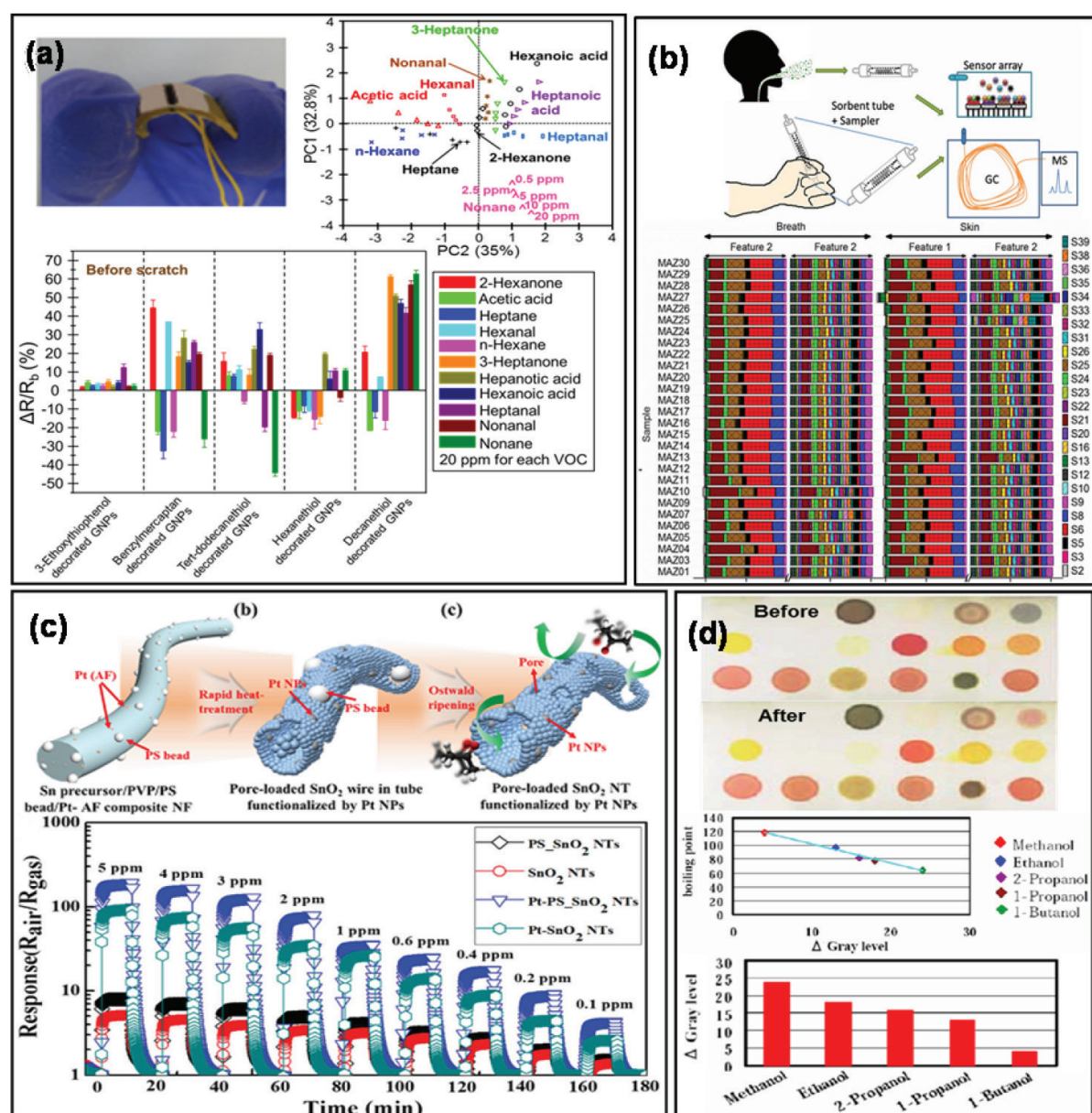


Figure 5. Typical examples of the practical and potential sensing elements for skin VOCs detection. (a) Functional group (at different chain-length) modified GNPs-based flexible device. (b) Combined volatolomics monitoring by nanomaterial-based devices. (c) Fiber-like SnO_2 for tracking trace amounts of VOCs. (d) A colorimetric VOCs device composed of different odor-responsive pigments. Reconstructed from Refs. 71, 78, 128 and [153, 163].

from human skin is expected to be non-invasive, real-time and operatable in non-clinical settings. These wearable devices can be managed either autonomically or remotely by a general practitioner. The concentration of these VOCs is normally at tens of ppb, suggesting high sensitivity and low LODs is required for these skin VOCs tracking sensors.

2.5.1. Metal nanoparticle-based resistometric sensors

In view of confirmation of the usability of metal nanoparticles [110, 113, 144, 145] in trace VOC detection, and other physical and environmental parameter monitoring (e.g. pressure, relative

humidity and temperature) [146], Segev et al. [78] developed a smart patch based on gold nanoparticle (GNP) film which gave a satisfactory performance. Based on this strategy, they developed series of analogous GNP-based devices for tracking VOC biomarkers extracted from human skin [54, 111]. **Figure 5a** shows 2 typical examples of a GNP-based device and its performance relative to several kinds of VOCs found in human skin/breath. Interestingly, an acceptable discrimination capability was observed for the device after combination with specific algorithms [54, 111]. To prove the feasibility of the GNP-based devices in practical healthcare application, Broza et al. [93] used the approach developed to monitor VOCs of skin samples (**Figure 5b**); they included a heterogeneous group of 30 volunteers with no acute or active disease. Although their main goal was to associate VOCs from skin and breath of specific volunteers, the second goal was to achieve a chemical profiling based on the VOC samples from either skin or breath. This method successfully created a unique chemical barcoding enabling classification and clustering of the volunteers, for example, clustering based on age-related VOCs.

2.5.2. Potential candidates for tracking skin VOCs

Several materials appear to be sensitive to VOCs from human breath and odor, as well as air pollutants. Although there is no direct evidence of the use of these materials to track VOCs from the skin, they have no great potential for the near future. Thus, a general description of these candidates is introduced in the following sub-sections.

2.5.2.1. Metal oxides

Gas-sensitive metal oxides can be divided into transition- and non-transition metal oxides [147]. It is generally believed that the former are more gas-sensitive than the non-transition metal oxides because of their more active chemical structure. Primary factors that influence sensing behavior of metal oxides include chemical components, surface area (surface-to-volume ratio), microstructures of sensing layers, humidity and temperature [148].

Generally, very few unitary metal oxides possess favorable properties for sensing VOCs, especially in tracing gas species at ppb level. For this level of sensitivity, recent studies have focused mainly on composites, that is, binary, ternary, quaternary or even more complex metal oxides (such as noble metal decorated metal oxides) [147, 148]. Details of the enhancement mechanism have been published [147–149]. Besides the chemical composition, materials with high surface-to-volume ratio (high surface area) provide more reaction sites. Fabrication of nanofibers by electrospinning (**Figure 5c**), generation of thin film by sputtering, as well as creating porous structures with help of pore forming agents, are the most popular ways of obtaining sensing candidates with a high surface area [150–153]. It has now been shown that, when the grain size is less than twice the thickness of surface charge layers, the grain is fully involved in the space-charge layer; consequently, gas sensitivity of the oxides can be significantly increased by adjusting grain size [149, 151]. Synthesis of oxides with unique shape and morphology is a very desirable method of enhancing the sensitivity of metal oxide gas sensors, as the shape and morphology of the oxides determines the crystallographic facets exposed on the surface of a nanocrystal, and will therefore determine the number of atoms located at the edges or corners [151]. By controlling the shape and

Materials	Synthesis routes	Morphology	BET surface area (m ² .g ⁻¹)	Response to 100 ppm ethanol	Temperature (°C)	Response time (s)	Refs.
SnO ₂	Thermal evaporation	Nanowire	N.M.	2.1	400	N.M	[154]
	Coprecipitation	Nonporous	19.5	13	300	13	[155]
	Electrospinning	Fiber	N.M.	15	340	10	[152]
	Hydrothermal	Nanosheets	31	35	270	13	[156]
	Coprecipitation	Microcubes	42.7	58	280	N.M.	[155, 157]
SnO ₂ /ZnO	Thermal evaporation and hydrothermal	hierarchical	N.M.	6	400	N.M	[154]
Ag-doped TiO ₂ /SnO ₂	Wet impregnation and nanocasting	Hierarchical flower	49	112.5	275	3.5	[158]

Table 3. Comparison of ethanol sensing performance, based on different SnO₂-based sensing materials.

morphology using different synthetic routes, the reactivity and selectivity of a nanocatalyst can be manually tailored.

One of the main challenges in metal oxide sensors is that water adsorption appreciably lowers the sensitivity of metal oxide gas sensors, since water adsorption on the metal oxide surface prevents donation of electrons to the sensing layers. Furthermore, prolonged exposure to humid environments leads to gradual formation of stable chemisorbed OH⁻ on the surface, resulting in progressive degradation. However, surface hydroxyls start to desorb at ~400°C so that the hydroxyl ions can be removed by heating to temperatures >400°C [151, 159]. Thus, an optimal operating temperature will essentially eliminate humidity interference. As the balance of adsorption/desorption is markedly affected by temperature, optimization of operating temperature improves the magnitude of response/recovery speed and response. **Table 3** lists several typical examples covering the above-mentioned strategies using SnO₂ as the sensing element [147, 150, 152, 154–158]. It is clear that shape/morphology, surface area and operating temperature influence the performance.

2.5.2.2. *Conducting polymers*

Conducting polymers (CPs) and their derivatives have been used as the active layers of gas sensors over the last century [160]. Compared to metal oxides sensors, devices made of conducting polymers have high sensitivities and short response durations at room temperature [161]. Conducting polymers are easily synthesized and their molecular chain structure can be conveniently modified by copolymerization or structural derivations [148, 161]. Furthermore, conducting polymers have good mechanical properties, which allow easy fabrication of sensor devices, and therefore considerable attention has been paid to these sensors.

Some of the earliest studies indicated that the sensing mechanism of CPs to VOCs involves swelling, namely the adsorbed VOC leads to the separation of polymer chains and increases

the hopping distance of charge carrier for charge transport. As a result, the electrical resistance (response signal) increases [148, 160, 161]. In some cases, polar VOC molecules behave as electron acceptors or donors contributing a charge carrier to the polymer, and subsequently participate as dopants that increase or decrease carrier concentration [148, 160]. Hybridization of CPs with inorganic and graphitic nanoscale building blocks, such as metal oxides, CNTs or graphene, are more advantageous in polymer processing [148]. These hybridized CPs can also provide tunable sensing performance to VOCs through hybridization of CPs with optimal nanoscale building blocks, furthering the design of advanced sensing devices for specific monitoring of VOC biomarkers.

2.5.2.3. Responsive dyes

Theoretically, if a VOC molecule interacts with a responsive dye, a visual response can be obtained by a change in color. Based on this working principle, colorimetric VOCs devices have been designed based on two fundamental requirements: (1) each chemically responsive dye must contain a center that strongly interacts with the analyte; (2) each interaction center must be strongly coupled to an intense chromophore. Metalloporphyrins (e.g. Cu(II), Zn(II), Mn(II), Co(III), Cr(III), Sn(IV)-based porphyrins, etc.) and some pH sensitive dyes (e.g. methyl red, bromophenol blue, chlorophenol red, etc.) are among the primary compositions for sensors based on responsive dyes [162]. Similarly, colorimetric devices showed their merits in identifying odorous biomarkers [163]. Following the interaction of VOCs with an array of responsive dyes, a unique color map was generated for each VOC and different color patterns could be seen at different concentrations of VOCs (**Figure 5d**) [163]. Combined with a specific algorithm, excellent discrimination was obtained. LODs of the colorimetric devices made of responsive dyes have generally ranged from hundreds of ppb to several ppm. Due to the strong interaction between VOC molecules and responsive dyes, this kind of device can often be very sensitive to VOC biomarkers. In summary, these disposable responsive dye-based colorimetric devices have given interesting results for consideration in the future of skin-based wearable devices.

3. Future perspectives

The rapid development of material science and engineering essentially stimulates progress in the development of wearable healthcare devices. Introduction of innovative sensing techniques has recently reformed our approach to disease diagnosis. It is undoubtedly reasonable to expect that real-time monitoring devices can give a much greater comprehensive assessment of the wearer's health status and improve his or her quality of life. Indeed, many more organizations are paying attention to this field since continuous personalized health monitoring using wearable healthcare devices that can be expected to provide low-cost solutions especially for remote monitoring, and will be particularly useful in indicating efficient treatment where early diagnosis can be made. To meet the market demands, extensive progress must be made in this field, which relies on the collaboration between material sciences and electronics, as well as sensing signal acquisition and processing. The requirement for highly active sensing

materials has spurred tremendous interests in developing monodisperse, single-component small-size NPs and encouraged researchers to put greater effort in searching for creative strategies in designing and synthesizing sensing elements with novel properties. Considering this goal, a better understanding of sensing mechanism can provide deep insight into the connection between sensing characteristics and materials composition/structure/morphology that will be instructive to scientists and engineers for exploring high-performance healthcare devices.

Although encouraging results have been achieved with a wide variety of wearable sensors, major obstacles remain that prevent the routine use of wearable devices by the general population. First, there is a lack of “bioaffinity” protocols [21], namely the relationship between these biomarkers and physiological index or a specific disease. Although some reports discuss this issue, the intrinsic connections remain ambiguous. Second, the precision, sensitivity, long-term stability and biocompatibility of devices must improve to meet the standard requirements from diagnostic devices, as defined by regulatory agencies. Third, there is a need to effectively reduce power consumption of these devices. In most situations, a sensing matrix should be built into these wearable devices for recording comprehensively body information, leading to considerable power consumption. Even though fabrication of self-powered devices suggests the way to solve this issue, power generation efficiency of this kind of devices remains questionable.

Although the importance of smart materials have been validated in designing high-performance, multifunctional, compact skin-based wearables, updates on the materials sciences still lags behind progress being made in the relevant fields. A typical example is that the biomaterials are less often reported in wearable healthcare devices, whereas this type of candidate will probably improve the current status. To date, biomaterials have been widely directed at their therapeutic applications; in particular they have shown unique features in the application of implantable healthcare devices [164, 165]. Owing to their natural biocompatibility and biodegradability, it is expected that skin-based wearable devices made of biomaterials will achieve even more unexpected results. One possible promotion is to replace the frequently used polymeric elastomer with more biocompatible biomaterials based substrates, for example, protein films, which will eliminate completely any irritation caused by the wearables. Their biodegradability will also be especially useful in designing environmental friendly products. As well as the more usual biomaterials, multifunctional materials also need more attention. As discussed in the section on multifunctional devices, these multifunctional materials that are spontaneously energy harvesting/self-healing and stimuli-responsive, or multi stimuli-responsive, will probably decrease the size, cost and the complexity of fabricating these healthcare devices. Although until now few relevant multifunctional candidates have been successfully devised, we speculate that wearables with smart multifunctional materials will lead to further innovative developments.

Overall, with advances in sensor sophistication and miniaturization, and battery solutions as well as materials sciences, much is expected to be packed into a patch. As with any wearable solution, there may need to be trade-offs in the number of data-points collected, the period of use and the processing power. Generally speaking, the closer the connection between the wearable device and the signal it is collecting, the greater will be the accuracy of the data. Because patches provide direct contact with the skin, they can detect very subtle changes in the patient's physiological condition and give comprehensive profile of one's health status.

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